

**APPLICATION FOR
UNITED STATES PATENT
IN THE NAME OF**

**ZIMING SUN
JAMES PARR
YI HSIN CHANG
UYEN UYEN HO
DARCY GEORGE**

FOR

STABILIZED ASCORBIC ACID COMPOSITION

DOCKET NO. 57095-5009

Prepared by

**JEFFER, MANGELS, BUTLER & MARMARO LLP
Tenth Floor
2121 Avenue of the Stars
Los Angeles, CA 90067
(310) 203-8080**

Express Mail No. EL891832630US

LADOC52741154 1

100133464
TOTAL 3200

STABILIZED ASCORBIC ACID COMPOSITION

This application is a continuation-in-part of U.S. Application Serial No. 09/224005, filed December 31, 1998.

5

Field of the Invention

The present invention relates to compositions for topical application that include ascorbic acid as an active ingredient.

Background of the Invention

10

Ascorbic acid, or Vitamin C (normally in the L-form) has been found to have three major biological functions with respect to the skin: to stimulate collagen synthesis in human skin fibroblasts; to act as an anti-oxidant to combat oxygen free radicals, which are stimulated by exposure to UV light, tobacco smoke and other environmental insults; and to act as an anti-inflammatory agent to control the inflammatory reaction associated with sunburn. Ascorbic acid acts to increase protein and collagen synthesis, with resulting anti-wrinkle effects, chelates with ferric ion to terminate oxygen-containing free radical processes, and prevents skin damage arising from excessive exposure to sunlight.

15

20

L-ascorbic acid is an alpha-ketolactone having the structure shown in Fig. 1. The number 2 and 3 carbons are double-bonded. L-ascorbic acid is stable in the solid state at ambient conditions. However, it is unstable in solution against oxidation and light degradation. Only a few days are required for a 5% ascorbic acid solution to completely decay into its oxidized form. In aqueous solution, L-ascorbic acid contains an ionizable hydrogen ($pK_1 = 4.17$ at room temperature). About 2.4% of ascorbic acid is deprotonated in a 2% aqueous solution at 25 °C.

25

Ascorbic acid is also a moderate reducing agent, since its redox potential is only +0.127 V at pH 5.0. The oxidation reaction of ascorbic acid is shown given in Fig. 1. Ascorbic acid lose two electrons to form the dehydrated form.

Express Mail No. EL891832630US

LADOC52741154 1

Two moles of protons are involved in the half-reaction; therefore the potential (electromotive force) of the half-reaction is pH dependent.

According to the Nernst equation,

$$E = E^0 + \left(\frac{RT}{nF}\right) \ln\left(\frac{[Vc(ox)][H^+]^2}{[Vc(red)]}\right)$$

- 5 (in which R is the ideal gas constant, F is the Faraday constant, E^0 is the standard electromotive force, $[Vc(ox)]$ is the concentration of oxidized ascorbic acid and $[Vc(red)]$ is the concentration of unoxidized ascorbic acid in the solution), potential is inversely proportional to the pH of the aqueous ascorbic acid solution. In the other words, when the pH is increased, the potential
- 10 decreases and the stability of ascorbic acid decreases. At pH 2 and 7, the calculated potentials E are 0.305 and 0.01 V, respectively, where $[Vc(ox)]$ and $[Vc(red)]$ are assumed to be 1 mol L^{-1} at 298.32 K. A plot of the pH dependence of the electromotive force for an ascorbic acid solution is given in Fig. 2. It is apparent that the deprotonated ascorbate anion is more susceptible to oxidation.
- 15 In view of the beneficial chemical and physical properties of ascorbic acid, many attempts have been made to stabilize ascorbic acid for topical application. The esterification of ascorbic acid was developed in early 1971. Stable derivatives of ascorbic acid were obtained by esterification. However, decreased activity was also observed. Ester derivatives of ascorbic acid have been used as
- 20 active ingredients in skin care creams as well as hair care products. A major disadvantage of such derivatives is their loss of antioxidative effectiveness due to the inability of the ester oxygen to chelate ferric ion.

Another approach involved stabilizing ascorbic acid in aqueous solution for topical application. Two different strategies have been developed for stabilizing

25 either anionic ascorbate at $\text{pH} > 4$ or the unprotonated form of ascorbic acid. U.S. Pat. Nos. 2,400,171 and 2,585,580 disclose that with monothioglycerol, calcium cation or zinc cation as well as calcium-aliphatic thiocarboxylic acid at $\text{pH} > 4$, stable compositions can be obtained. However, the anionic ascorbate is

unfavorable for penetrating the skin, and is also more unstable than the un-ionized form for topical application because of the higher potential of the ascorbate anion (see Fig. 2).

Current research efforts are directed to stabilization of the un-ionized form of ascorbic acid for topical application. U.S. Pat. Nos. 5,736,567, 5,703,122 and 5,691,378 disclose that ascorbic acid can be stabilized over time by limiting water activity to below 0.85 using polyols. Didier and Nathalie (U.S. Pat. Nos. 5,629,004 and 5,552,446) also disclose incorporating ascorbic acid solution into a water-in-oil (w/o) emulsion to extend the life span of ascorbic acid.

The instability of ascorbic acid in aqueous solution is due to its structural alpha-keto frame, its interaction with water, and also due to oxygen permeating into the solutions. Stabilization of the anionic form or reduction of the water activity are insufficient to afford the desired stability. In order to adequately increase the stability of ascorbic acid in aqueous solution for topical application, all of the foregoing effects must be taken into consideration.

A continuing need exists for a stabilized ascorbic acid composition suitable for topical application.

Summary of the Preferred Embodiments

In accordance with one aspect of the present invention, there is provided a composition that includes (a) about 2 to about 25 wt % of L-ascorbic acid, (b) about 0.1 wt% to about 10 wt % of at least one selected form the group consisting of cationic polymers and cationic surfactants, and (c) about 0.1 wt% to about 70 wt % of at least one selected from the group consisting of humectants, polymers with humectant properties and inorganic driers. In the composition, the ratio of ingredient (a) to ingredient (b) is about 1:1 to about 50:1. The composition is stable when stored at room temperature for a period of at least ten weeks.

Emulsions containing the inventive compositions in the water phase are also provided, as are methods for preparing the inventive compositions.

Other objects, features and advantages of the present invention will become apparent to those skilled in the art from the following detailed description. It is to be understood, however, that the detailed description and specific examples, while indicating preferred embodiments of the present invention, are given by way of illustration and not limitation. Many changes and modifications within the scope of the present invention may be made without departing from the spirit thereof, and the invention includes all such modifications.

Brief Description of the Drawings

The invention may be more readily understood by referring to the accompanying drawings in which

FIG. 1 is an illustration of two chemical reactions for ascorbic acid in aqueous solution.

FIG. 2 is a plot of the pH dependence of the electromotive force of an ascorbic acid solution, calculated using the Nernst equation, wherein $[Vc(ox)]$ and $[Vc(red)]$ were assumed to be 1.0 mol L^{-1} .

FIG. 3 is a plot of concentration (wt%) vs. time (weeks) for ascorbic acid solutions according to Examples 1, 6, 11 and 16 herein at 25°C (open symbols) and 40°C (closed symbols), respectively, wherein the concentrations were obtained by colorimetric analysis.

Detailed Description of the Preferred Embodiments

The present invention provides stable ascorbic acid compositions for topical application. Particular embodiments of the invention are specially designed for cosmetic and dermatological products. In particular, the invention is directed to skin-care and skin-treatment products, as well as processes to incorporate the compositions into water-in-oil (w/o), oil-in-water (o/w), and water-in-oil-in-water (w/o/w) emulsions. By employing cationic polymers or cationic surfactants to form complexes with both un-ionized and ionized forms of ascorbic acid, and decreasing water activity by using humectants and/or inorganic driers so as to

limit oxygen permeability into water, highly stable topical compositions are provided.

As used herein, an ascorbic acid composition is "stable" if the concentration of ascorbic acid in the composition does not decrease by more than 5% after
5 storage at 25°C for a period of ten (10) weeks.

When ascorbic acid is dissolved in water in a 2% solution, about 2.4% of the ascorbic acid is ionized to form anionic ascorbate, and the ionized and un-ionized forms are in equilibrium (see Fig. 1). Through controlling the water activity to reduce water mobility and oxygen permeability, a more stable ascorbic acid
10 solution is obtained. However, the ionized form is still readily oxidized. In order to stabilize the ascorbic acid solution for an extended period of time, both the ionized and un-ionized forms must be considered at the same time. If the ionized form is slowly oxidized over time, more of the un-ionized form will be ionized to maintain the equilibrium.

By introducing cationic polymers or cationic surfactants that can form complexes with both the ionized and un-ionized forms of ascorbic acid, together with humectants that reduce the water activity and the permeation of oxygen into the aqueous solution, highly stable topical compositions are produced. All of the influences on stability discussed above are taken into consideration in the
20 inventive compositions. As a result, the inventive aqueous solutions are very stable over the course of time.

The inventive compositions are capable of stabilizing ascorbic acid over a wide range of pH (about 2 to about 7) by controlling the ratio of ascorbic acid to cationic polymers and/or cationic surfactants. As an extra beneficial feature, the
25 inventive compositions have an elegant feeling when applied to the skin and are less irritating, making the compositions very suitable for use in skin-care and skin-treatment products.

When materials (solutes) are dissolved in water to form a diluted ideal solution, the molecules of the various species components are so similar to one

another that molecules of one component can replace molecules of another component in the solution without changing the solution's energy or spatial structure. In other words, the molecules of solute and solvent resemble one another closely in size, shape and intermolecular interactions. Therefore, the

5 activity of water molecules can be described by Raoult's Law, $P_A = x_A P_A^*$, where P_A and P_A^* are vapor pressures for aqueous solution and pure water at constant temperature, respectively; x_A is water activity, $x_A = n_A / (n_A + n_B)$, where n_A is the number of moles of water and n_B is the number of moles of solute. The water activity is determined by measuring the vapor pressure of the solution.

10 If, however, the size, shape and/or intermolecular interactions of water and the solute are different, then deviations from Raoult's Law will be observed. If the interaction between molecules of the solute and molecules of water is stronger than the interaction between the molecules of water, as well as stronger than that between the molecules of solute, a negative deviation from Raoult's Law
15 will be observed. In other words, lesser amounts of solute will cause great decreases in water activity.

The humectants preferably used in the inventive compositions are able to form multiple hydrogen bonds with molecules of water. Thus, large negative deviations from Raoult's Law are usually observed in aqueous solutions including
20 the humectants. The decreased water activity results in less mobility of free water molecules and decreased oxygen permeability into the water.

Exemplary cationic polymers and cationic surfactants that are usefully employed in compositions according to the invention include, without limitation, polyquats such as polyquaternium 2, polyquaternium 4, polyquaternium 6,
25 polyquaternium 7, polyquaternium 10, polyquaternium 11, polyquaternium 16, polyquaternium 17, polyquaternium 18, polyquaternium 22, polyquaternium 24, polyquaternium 27, polyquaternium 28, polyquaternium 39, polyquaternium 42 and polyquaternium 46 and mixtures thereof.

Quaternized cellulose, collagens and proteins are also cationic polymers that are beneficially employed in embodiments of the inventive compositions. These include, without limitation, guar hydroxypropyltrimonium chloride, lauryldimonium hydroxypropyl oxyethyl cellulose, lauryldimonium hydroxyethyl cellulose,

5 lauryldimonium hydroxypropyl hydrolyzed silk, protonated polyethylenimine, hydrolyzed casein, cocodimonium hydroxypropyl oxyethyl cellulose, cocodimonium hydroxypropyl hydrolyzed collagen, cocodimonium hydroxypropyl hydrolyzed hair keratin, cocodimonium hydroxypropyl hydrolyzed keratin, cocodimonium hydroxypropyl hydrolyzed wheat protein, stearyldimonium
10 hydroxyethyl cellulose, stearyldimonium hydroxypropyl hydrolyzed collagen, stearyldimonium hydroxypropyl hydrolyzed wheat protein, stearyldimonium hydroxypropyl oxyethyl cellulose, stearyltrimonium hydroxyethyl hydrolyzed collagen, lauryl methyl gluceth-10 hydroxypropyldimonium chloride, oleyl betaine and cocamidopropyl betaine.

15 Cationic surfactants that can be employed according to the invention include, without limitation, cetrimonium chloride, cetrimonium bromide, dicetyldimonium chloride, acetamidopropyl trimonium chloride, behentrimonium chloride, hydroxyethyl cetyldimonium chloride, cetalkonium chloride and mixtures thereof.

Humectants and/or inorganic driers beneficially employed in embodiments of
20 the inventive composition include, without limitation, glycerol, sorbitol, panthenol, 1,2-propylene glycol, 1,3-butylene glycol, sodium lactate, potassium lactate, magnesium lactate, calcium chloride, magnesium sulfate and mixtures of thereof.

Polymers with humectant properties are useful in combination with cationic
25 polymers and/or cationic surfactants. Examples of useful polymers with humectant properties include, without limitation, PVP/MA copolymer, PVP/MA decadiene crosspolymer, PVP, PVP/dimethylaminoethyl methacrylate copolymer, PVP/dimethylaminoethyl methacrylate/polycarbamyl polyglycol ester, PVP/dimethiconylacrylate/polycarbamyl polyglycol ester, PVP/polycarbamyl

polyglycol ester, PVP/VA copolymer, hydroxyethyl cellulose, hydroxypropyl guar, hydroxypropylmethyl cellulose, hydroxypropyl cellulose, polyethylene glycol 200, polyethylene glycol 300, polyethylene glycol 400, polyethylene glycol 600, polyethylene glycol 900, polyethylene glycol 1000, polyethylene glycol 1450, methyl glucose sesquiosostearate, methyl gluceth-10, methyl gluceth-20, PPG-10 methyl glucose ether, PPG-20 methyl glucose ether, PPG-20 methyl glucose ether distearate, and mixtures thereof.

In preferred embodiments of the inventive composition, metal sequestering agents, such as salts of EDTA, are also used for chelating ferric and manganese ions that are often present in water, since both of these ions are capable of accelerating the oxidation of ascorbic acid.

Preferred embodiments of the inventive composition are multiphase emulsions, such as w/o, o/w and w/o/w emulsions. Exemplary oil components for multiphase emulsion embodiments include, without limitation, silicone oils, mineral oil, peanut oil, soy oil, olive oil, wheat germ oil, avocado oil, castor oil, Jojoba oil and synthetic esters by direct reaction of fatty acids with alcohols. More specific examples of synthetic esters include isopropyl esters, ethylhexyl esters, oleic acid esters, caprylic/capric acid esters, N-butyl stearate, isocetyl stearate, octyldodecanol, diisopropyl adipate and pentaerythritol tetraistearate.

Emulsifiers and stabilizers useful in embodiments of the inventive composition include, without limitation, sodium cocyl isothionate, potassium cetyl phosphate, ethoxylate fatty alcohol, PEG esters of fatty acids, ethoxylated sorbitan esters, ethoxylated monoglycerides, ethoxylated castor oil derivatives, sorbitan monooleate, sorbitan sesquioleate, glycerol monooleate, polyglycerol esters, oleate, ricinoleates, isostearate, methoxy PEG-22 dodecyl glycol copolymer, lanolin derivatives, polyacrylate resins, acrylamide/sodium acrylate copolymer and PEG-45 dodecyl glycol copolymer.

The quantity of cationic polymers and/or cationic surfactants used in the inventive composition is about 0.1 wt% to about 10 wt%, preferably 0.2 wt% to

5 wt% depending on the specific individual cationic polymer and/or cationic surfactant, more preferably 0.3 wt% to 2 wt% for polyquaternium 6 as the cationic polymer. The quantity of humectant(s) is about 1 wt% to about 70 wt%, preferably 5 wt% to 40 wt%, more preferably 20 wt% to 30 wt% when polyquaternium 6 is used in the inventive composition. The quantity of polymer(s) with humectant properties used to assist the cationic polymers and/or cationic surfactants is about 0.1 wt% to about 15 wt%, preferably 0.5 wt% to 5 wt%, more preferably 0.5 wt% to 1 wt% when polyquaternium 10 (JR 400) is used. When inorganic driers are used, the quantity thereof is about 0.1 wt% to about 1 wt%, preferably 0.2 wt% to 1 wt%, more preferably 0.2 wt% to 0.3 wt%. The amount of sequestering agent, when used, is preferably less than 0.1 wt%. The oil phase in w/o, o/w and w/o/w emulsion embodiments of the inventive composition preferably constitutes about 15% to about 50%, depending upon the type of emulsion.

15 A classical colorimetric assay (Day et al, Clin. Biochem. 1979, 12, pp22-26) has been used for determining the content of the ascorbic acid in aqueous compositions over the time. The assay is based upon the quantitative reduction of the ferric complex of 2, 4, 6-tripyridyl-s-triazine by ascorbic acid to a purple colored ferrous complex of 2, 4, 6-tripyridyl-s-triazine in a buffer solution of acetic acid-acetate. As the reaction takes place, the solution changes color from almost colorless to purple, which is detected at 595 nm on a UV spectrophotometer. The oxidized dehydro ascorbic acid does not react with ferric complexes of 2, 4, 6-tripyridyl-s-triazine and does not interfere with the determination.

25 The invention is further illustrated by the following non-limiting examples. The composition solutions are stored in light-impermeable bottles or jars for stability tests. The ascorbic acid content is determined by colorimetry over time for ten weeks at both room temperature and 40 °C. Stability data are set forth in Table 1.

EXAMPLE 1

	d.i. water	25.94%
	polyquaternium-6 (40%)	2.17 %
	tetrasodium EDTA	0.05%
5	L-ascorbic acid	2.0%
	10% sodium hydroxide	4.54%
	panthenol	0.3%
	propylene glycol	65%
	The pH is 6.65 at room temperature	

10

EXAMPLE 2

	d.i. water	23.47%
	polyquaternium-24	0.5%
	tetrasodium EDTA	0.05%
15	L-ascorbic acid	5.0%
	10% sodium hydroxide	5.68%
	panthenol	0.3%
	butylene glycol	65%
	The pH is 4.95 at room temperature	

20

EXAMPLE 3

	d.i. water	30.65%
	cocodimonium hydroxypropyl	
	oxyethyl cellulose	4.0%
25	tetrasodium EDTA	0.05%
	panthenol	0.3%
	L-ascorbic acid	5.0 %
	butylene glycol	60%
	The pH is 3.12 at room temperature.	

EXAMPLE 4

	d.i. water	25.59%
	acetamidopropyl	
	trimonium chloride	2.21%
5	disodium EDTA	0.05%
	L-ascorbic acid	2.0%
	10% sodium hydroxide	4.45%
	panthenol	0.3%
	butylene glycol	65%
10	The pH is 6.39.	

EXAMPLE 5

	d.i. water	27.36%
	polyquaternium-2	1.5%
15	tetrasodium EDTA	0.05%
	PVP/VA	2.0%
	panthenol	0.3%
	ascorbic acid	5.0%
	10% sodium hydroxide	3.785%
20	propylene glycol	60%
	The pH is 4.55.	

EXAMPLE 6

	d.i. water	29.15%
25	polyquaternium-10 (JR-30M)	0.5%
	tetrasodium EDTA	0.05%
	panthenol	0.3%
	L-ascorbic acid	5.0%
	propylene glycol	65%

The pH is 3.21.

- Polyquaternium-10 (0.5 g) is dissolved in 29.15 g d.i. water and the solution is warmed to 60 °C for hydration. The solution is cooled to room temperature and
- 5 the other ingredients are added.

EXAMPLE 7

	d.i. water	66.95%
	disodium EDTA	0.05%
10	polyquaternium-11	2.0%
	sorbitol	5.0%
	panthenol	0.5%
	L-ascorbic acid	10.0%
	PEG-4	15%
15	magnesium sulfate	0.5%
	The pH is 2.06.	

EXAMPLE 8

	d.i. water	32.73%
	polyquaternium-10 (JR-400)	0.4%
	PVP	1.5%
5	disodium EDTA	0.07%
	panthenol	0.3%
	L-ascorbic acid	15%
	propylene glycol	50%
	pH at 2.46.	

10

EXAMPLE 9

	d.i. water	32.93
	polyquaternium-10 (JR-125)	0.2%
	PVP	1.5%
15	disodium EDTA	0.07%
	L-ascorbic acid.	15.0%
	panthenol	0.3%
	propylene glycol	35%
	PEG-4	15%
20	The pH is at 2.51.	

EXAMPLE 10

	d.i. water	59.63%
	hydroxypropyl guar	
25	hydroxypropyltrimonium chloride	0.3 %
	disodium EDTA	0.07%
	PVP [poly(vinylpyrrolidone)]	0.7%
	L-ascorbic acid	15%
	panthenol	0.3%

glycerin 15%
PEG-4 10%

The pH is 2.20.

- 5 0.3 g of hydroxypropyl guar hydroxypropyltrimonium chloride is added to 50 g of d.i. water and hydrated by heating the solution to 60 °C. After the solution is cooled to room temperature, the other ingredients are added.

EXAMPLE 11

10 d.i. water 64.63%
disodium EDTA 0.07%
polyquaternium-27 3.0%
PVP 2.0%
panthenol 0.3%
15 L-ascorbic acid 20.0%
PEG-4 10.0%
The pH is 2.07.

EXAMPLE 12

20 A. L-ascorbic acid 1%
propylene glycol 99%
B. L-ascorbic acid 1%
Ethoxydiglycol 99%

25 EXAMPLE 13

d.i. water 74.95%
disodium EDTA 0.05%
stearyldimonium hydroxypropyl
oxyethyl cellulose (20-24%) 15%

L-ascorbic acid 10%

pH is 2.28 at room temperature.

EXAMPLE 14

d.i. water 94.95%

5 disodium EDTA 0.05%

polyquaternium-10 (JR-400) 0.1%

L-ascorbic acid 0.5%

pH is 2.85 at room temperature.

10 EXAMPLE 15

Water phase

d.i. water 29.23%

disodium EDTA 0.058%

PEG-4 12.42%

15 polyquaternium-28 2.65%

L-ascorbic acid 12.42%

butylene glycol 12.42%

panthenol 0.3%

Silicone oil phase

20 Dow Corning 3225 fluid TM

(cyclomethicone, dimethicone

copolyol) 10.0%

gel aid 8717 TM

(cyclomethicone, cyclomethicone,

25 dimethicone) 15%

Rhodorsil 45v5 TM

(cyclomethicone) 5%

PPG-3 myristyl ether 0.5%

The water phase is added to the oil phase slowly with turbulent mixing. A gel-like composition is formed.

EXAMPLE 16 (oil in water)

5	water phase	
	d.i. water	73.25%
	disodium EDTA	0.05%
	salicylic acid	0.30%
	polyquaternium-4	1.00%
10	L-ascorbic acid	5.00%
	glycerin	3.00%
	panthenol	0.30%
	sepigel	1.50%
	sodium cocoyl isethionate	1.0%
15	oil phase	
	stearyl alcohol	1.5%
	cetyl alcohol	1.0%
	steareth-21	1.25%
	steareth-20.	1.25%
20	PEG-100 stearate	0.5%
	PEG-20	1.0%
	PPG-15 stearyl ether	8.0%
	Fragrance	0.1%

25 EXAMPLE 17

	phase A	
	d.i. water	13.12%
	disodium EDTA	0.01%
	polyquaternium-6	0.20%

	magnesium sulfate	0.06%
	L-ascorbic acid	3.9%
	butylene glycol	3.0%
	panthenol	0.12%
5	phase B	
	Dow Corning 200 fluid 50cts	
	(dimethicone)	0.9%
	Dow Corning 246 (cyclomethicone)	0.9%
10	gel aid 8717 TM (cyclomethicone, cyclomethicone, dimethicone)	1.05%
	Rhodorsil 45v5 TM	
	(cyclomethicone)	5.85%
	Abil EM-97	
15	(dimethicone copolyol, cyclopentasiloxane)	0.9%
	phase C	
	Add phase A into phase B	
	slowly to form w/o phase	
20	Sepigel	3.0%
	phase D	
	d.i. water	46.5%
	butylene glycol	20.0%
	polysorbate-20	0.5%

25

Add Sepigel into w/o phase slowly and add phase D into phase C rapidly. The stable triple phase can be seen under a microscope and detected by conductivity measurement.

Examples 1-6 explore the pH-dependent stability of the composition by keeping other ingredients at almost constant levels. To simplify the examination, only one cationic surfactant (or one cationic polymer) and one humectant are used in each formula.

5 Two results are observed from the stability data obtained at different pH:

(1) More degradation is observed in high pH solutions than in low pH solutions. But overall, after two month, only a slight degradation of ascorbic acid was observed for these compositions at room temperature. The experimental data are in agreement with the plot of pH-dependent electromotive force shown in Fig. 2.

(2) Three different cationic polymers or cationic surfactants were used to stabilize the ascorbic acid solutions. The stability data show that they profoundly increase the stability of the ascorbic acid in aqueous solution. The experimental data are also in agreement with the plot of pH-dependent electromotive force shown in Fig. 2.

Examples 7-11 explore the possibility of using high concentrations of ascorbic acid solution and also varying the water content in the compositions. All compositions are very stable at room temperature; the extent of degradation observed from the stability data over eight weeks is negligible.

20 Examples 12(A) and 12(B) test polyols to stabilize the ascorbic acid alone. As the data in Table 1 show, noticeable degradation (more than 10%) is evident over the course of one month at room temperature. The results indicate that polyols by themselves can stabilize ascorbic acid, but cannot provide very stable compositions.

25 For comparison, example 13 tests the stability of ascorbic acid aqueous solution with a cationic polymer alone. The stearyldimonium hydroxypropyl oxyethyl cellulose is the only agent for stabilizing the ascorbic acid. The stability data at room temperature and at 40 °C for two weeks are very close, and only slight degradation is observed for the sample. The results strongly suggest that

the cationic polymer forms complexes with ascorbic acid to stabilize the ascorbic acid in aqueous solution. Since both the cationic polymers and humectants are able to stabilize the ascorbic acid aqueous solution to a great degree, compositions containing both of these components are optimal for stabilizing ascorbic acid in aqueous solution.

Example 14 illustrates a solution having lower concentrations of ascorbic acid and cationic polymers. The ascorbic acid degraded more rapidly than in other examples (see Table 1). About 20% of the ascorbic acid oxidized at room temperature in two weeks.

The stability at 40 °C is also determined for seven other examples (listed in Table 1). The data for examples 1, 6, 11 and 16 are plotted in Fig. 3. In Fig. 3, room temperature data (open symbols) and data at 40 °C (filled symbols) are plotted together for comparison. At 40°C, the apparent degradation is noticeable for example 1. This is attributable to the relatively high pH of the composition (pH 6.65). Slight degradation is found for example 11, which is attributable to the lower humectant content. Insignificant degradation is observed for example 6 at both room temperature and 40°C, which may be due to the combination of a large amount of humectants and cationic polymers.

The water-in-oil (w/o), oil-in-water (w/o) and water-in-oil-in-water (w/o/w) emulsions are also designed for further increasing the stability of ascorbic acid solution for topical application. For all of these examples, unnoticeable degradation is observed even at 40 °C for two weeks. When a stable ascorbic acid solution is encapsulated in the oil phase, the most stable compositions are obtained. Essentially unnoticeable degradation of ascorbic acid is observed in example 17 at 40 °C over five weeks.

Table 1

Example	[A] ₁	pH	[A] _{5,RT}	[A] _{10,RT}	[A] _{2,40}	[A] _{5,40}
1	2.0	6.65	1.98	1.75	1.48	1.01
2	5.0	4.95	4.97	4.52		
3	5.0	3.12	5.20	5.15		
4	2.0	6.39	1.94	1.89		
5	5.0	4.55	4.97	5.01		
6	5.0	3.21	5.08	5.05	5.12	5.00
7	10.0	2.34	10.16		10.03	
8	15.0	2.46	15.20	15.05		
9	15.0	2.51	15.10	15.04		
10	15.0	2.20	15.21	15.19		
11	20.0	2.06	20.24	20.01	19.32	18.90
12(A)	1.0		0.89	0.76		
12(B)	1.0		0.85	0.73		
13	10.0	2.29	10.12		9.30	
14	0.5	2.85			0.30	
15	12.42		12.57		12.40	12.04
16	5.0	2.35	5.06			
17	3.9		3.91		3.80	3.83

[A]₁ = initial ascorbic acid concentration, %

[A]_{5,RT} = ascorbic acid concentration after 5 weeks, room temperature

[A]_{10,RT} = ascorbic acid concentration after 10 weeks, room temperature

25 [A]_{2,40} = ascorbic acid concentration after 2 weeks, 40°C

[A]_{5,40} = ascorbic acid concentration after 5 weeks, 40°C